



Postoperative Pancreatic Fistula in Surgery for Perihilar Cholangiocarcinoma

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Abstract

Background There are numerous studies on postoperative pancreatic fistula (POPF) in pancreatic surgery but few studies on POPF in extrahepatic bile duct resection with or without hepatectomy for perihilar cholangiocarcinoma (PHCC). The aim of this study is to investigate the incidence of and risk factors for POPF in this challenging surgery.

Methods All consecutive patients who underwent surgical resection for presumed PHCC between January 2008 and December 2017 were retrospectively reviewed, with special attention paid to POPF.

Results Among 416 patients, 90 patients showed a drain amylase level of > 3 times the normal limit on day 3 or after. The severity of POPF was biochemical leakage in 46 patients and grade B in 44 patients. No patient had grade C POPF; thus, the incidence of clinically relevant POPF was 10.6% (44/416). The resection line of the common bile duct was closely associated with POPF; 23 (27.7%) of the 83 patients who underwent intrapancreatic resection of the common bile duct developed POPF. The occurrence of intra-abdominal abscess and liver failure was significantly higher in patients with POPF, but the 90-day mortality was similar. The multivariate analysis identified a body mass index of ≥ 22 and intrapancreatic bile duct resection as independent risk factors for POPF.

Conclusions POPF occurs in approximately 10% of patients undergoing resection for PHCC. Careful postoperative management with attention to POPF is required, especially in patients who undergo intrapancreatic resection of the common bile duct and in those with a high body mass index.

Introduction

Surgery for perihilar cholangiocarcinoma (PHCC) is technically demanding and highly associated with postoperative complications, even in leading centres [1–3]. The standard curative-intent resection is hepatectomy combined with extrahepatic bile duct resection and bilio-enteric reconstruction [1]. In this type of resection, the common bile duct is usually divided at the superior margin of the

pancreas head, while the duct is sometimes excavated and divided at the intrapancreatic level due to downward cancer extension [1, 2]. In addition, dissection of the regional lymph nodes around the pancreas head is routinely performed. These procedures may potentially injure the pancreatic parenchyma, which leads to postoperative pancreatic fistula (POPF). POPF is frequently associated with surgical site infection and considered a major, troublesome complication in pancreatic surgery. Although there are a great number of studies on POPF in pancreatic surgery [4–6], to our knowledge, only one study reported POPF in surgery for PHCC [7]; thus, little is known on this issue.

The aim of the present retrospective study is to review the authors' experiences of surgery for PHCC and to

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investigate the incidence of and risk factors for POPF in this surgery.

Methods

Patients

Between January 2008 and December 2017, all consecutive patients who underwent extrahepatic bile duct resection with or without hepatectomy for presumed PHCC in the First Department of Surgery at Nagoya University Hospital were retrospectively reviewed, focusing on POPF. The study was approved by the Human Research Review Committee of Nagoya University Hospital (Approval No. 2018-0393).

Preoperative management

Details regarding preoperative management were described in the previous report [1]. In brief, dynamic computed tomography and cholangiography were routinely performed as a preoperative workup. Percutaneous or endoscopic biliary drainage was performed in patients who had jaundice and/or dilated bile ducts in the future liver remnant [8, 9]. Portal vein embolization was conducted when the liver remnant was estimated to be less than 40% [10].

Surgery

Surgeries were performed once the total serum bilirubin concentration was less than 2 mg/dL. The type of hepatectomy was determined according to the location of the primary tumour, as previously reported [1]. The common bile duct was usually divided at the superior margin of the pancreas head (Fig. 1a). If the downward extension of cancer was suspected, the duct was excavated and divided

at the intrapancreatic level (Fig. 1b). When the examination of an intraoperative frozen section of the bile duct (distal ductal margin) was positive, an additional resection of the intrapancreatic bile duct or pancreatoduodenectomy was considered [11]. The intrapancreatic bile duct was dissected by instrument crash clamping with electric cautery. We did not use coverage using the omentum or round ligament of the defected area of the pancreatic parenchyma after intrapancreatic bile duct resection.

All patients underwent regional lymph nodes dissection, including proper hepatic artery (denoted as “12a” by General rules for surgical and pathological studies on cancer of the biliary tract [12]), pericholedochal (“12b” and “12c”), hilar (“12 h”), periportal (“12p”), peripancreatic (“13a”), and common hepatic artery (“8a” and “8p”) nodes (Fig. 2). For periaortic lymph nodes, the sampling of only two or three nodes was performed for staging. The liver parenchyma was transected using the cavitron ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, Colorado, USA) under both hepatic artery and portal vein clamping for 15 or 20 min at 5-min intervals.

Bilio-enteric anastomosis was performed by Roux-en-Y cholangiojejunostomy as previously reported [13]. Three closed abdominal drains were routinely placed along the liver transection plane, near the bilio-enteric anastomosis and behind the pancreas head (Fig. 3) [14].

Postoperative drain management

The amylase and total bilirubin values of the drainage fluid were measured on postoperative days 1, 3, and 7 until the drains were removed [15]. Drain fluid was also sampled for a surveillance culture at the same time [16]. If the drainage fluid appearance was clear, the drains were to be removed within 7 days. Drains placed for more than 10 days after surgery were exchanged for a new drainage tube. Thereafter, the drains were exchanged once or twice a week until

Fig. 1 Intraoperative photos. **a** The common bile duct was divided at the level of pancreatic entry. **b** The pancreatic parenchyma was excavated to resect the common bile duct at the intrapancreatic level (white arrow heads)

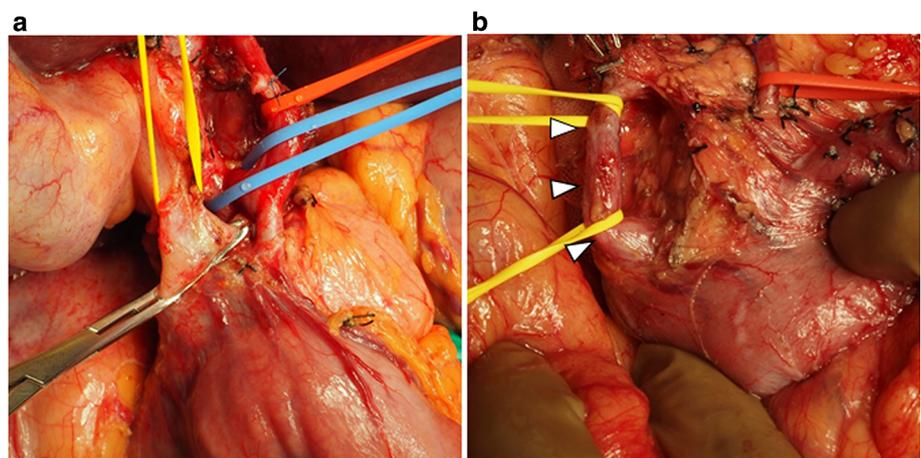


Fig. 2 Intraoperative photos before (a) and after (b) peripancreatic node dissection. White and black arrows indicate No12b and No13a lymph nodes, respectively. White arrow heads indicate the stump of the common bile duct which was closed by running suture. In this “thin” patients, node dissection was performed without pancreatic parenchyma injury. CBD, common bile duct; PV, portal vein

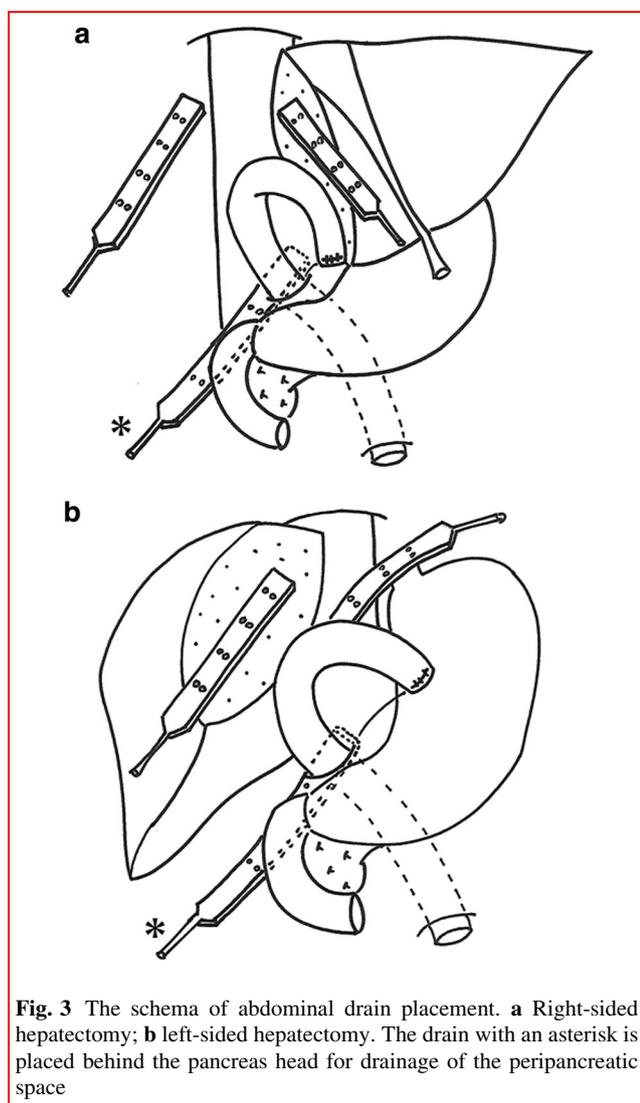
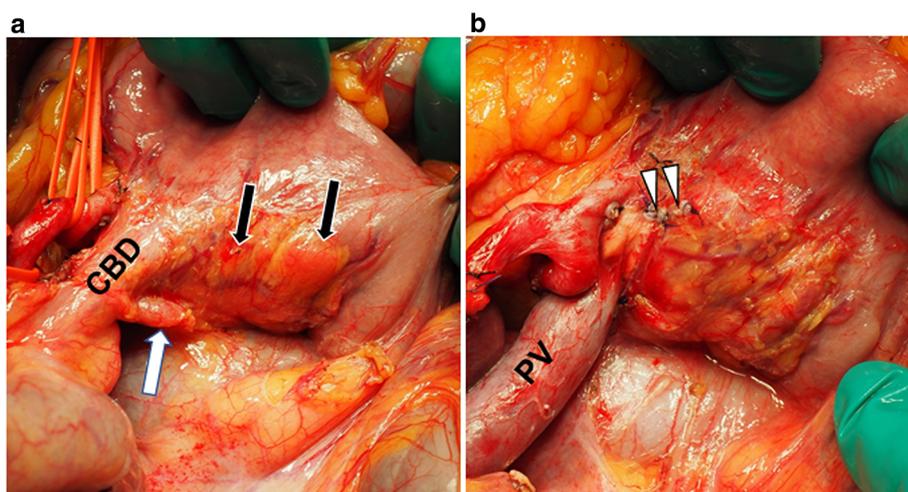


Fig. 3 The schema of abdominal drain placement. **a** Right-sided hepatectomy; **b** left-sided hepatectomy. The drain with an asterisk is placed behind the pancreas head for drainage of the peripancreatic space

removal [14]. Computed tomography was conducted on postoperative day 7 in all patients, to detect abnormal fluid collection.

POPF was classified according to the International Study Group of Pancreatic Surgery (ISGPS) [4]. Bile leakage and postoperative liver failure were defined according to the International Study Group of Liver Surgery (ISGLS) [17].

Statistics

Results are expressed as the medians (ranges) for continuous data, unless otherwise specified. The statistical analysis was performed with the Mann–Whitney *U* test for continuous variables and the Chi-squared test or Fisher’s exact probability test for categorical variables. Continuous variables were dichotomized according to a receiver operating characteristic (ROC) curve analysis. A multi-variable analysis was performed using the logistic regression model to identify risk factors for POPF. Values of $P < 0.05$ were considered significant. All statistical analyses were conducted using SPSS for Windows version 21 (IBM Japan Inc., Tokyo, Japan).

Results

Study patients

During the 10-year study period, a total of 486 consecutive patients underwent resection with a clinical diagnosis of presumed PHCC. Of these, 65 patients who underwent combined pancreatoduodenectomy and one patient who underwent combined distal pancreatectomy were excluded because this study focused on surgery without pancreatectomy. Four additional patients who had previous biliary

surgery were also excluded. The remaining 416 patients, including 285 men and 131 women with a median age of 69 years (range 34–89 years), were enrolled.

Surgery performed

Of the 416 analysed patients, 411 (98.8%) patients underwent major hepatectomy (resection of ≥ 3 Couinaud's hepatic segments) with caudate lobectomy, and the remaining 5 patients underwent extrahepatic bile duct resection alone. The common bile duct was divided at the superior border of the pancreas in 333 (80.0%) patients and at the intrapancreatic level in the remaining 83 (20.0%) patients. Of the latter 83 patients, 15 patients underwent additional resection of the intrapancreatic bile duct due to positive distal margin by frozen section examination. A combined resection of the portal vein and/or hepatic artery was performed in 175 (42.1%) patients. The final pathology was PHCC in 407 (97.8%) patients and benign bile duct stricture in the remaining 9 patients.

Incidence and characteristics of clinically relevant POPF

In 90 (21.6%) patients, the amylase level of the abdominal drain placed behind the pancreas head (Fig. 1) was 375 IU/L or more (3 times the upper limit of the institutional normal range of serum amylase) on postoperative day 3 or after. According to the ISGPS definition [4], the severity of POPF was biochemical leakage in 46 patients and grade B in 44 patients. No patient had grade C POPF. Thus, the incidence of clinically relevant POPF (grade B) was 10.6% (44/416).

Patient characteristics are summarized according to those with POPF ($n = 44$) or without POPF ($n = 372$) in Table 1. The resection line of the common bile duct was closely associated with POPF. Of the 83 patients who underwent intrapancreatic resection of the common bile duct, grade B POPF occurred in 23 patients (27.7%). This incidence was significantly high compared to the 333 patients who had resection at the pancreatic entry (6.5%). Body mass index (BMI) and operative time were also significantly greater in patients with POPF. No between-group differences were observed in regard to other clinical variables. ROC curve analysis revealed that the optimal cutoff value of BMI to predict POPF was 22 kg/m² (area under the curve: 0.595).

Postoperative outcome

Although fairly obvious, the amylase levels of the abdominal drain on days 1, 3, and 7 were significantly higher in patients with POPF (Table 2). The positivity rates

Table 1 Patient characteristics according to with or without clinically relevant pancreatic fistula

Variables	Pancreatic fistula		P
	Without ($n = 372$)	With ($n = 44$)	
Age [years]	69 (34–89)	71 (41–85)	0.163
Gender, n (%)			0.327
Male	252 (67.7)	33 (75.0)	
Female	120 (32.3)	11 (25.0)	
Body mass index [kg/m ²]	21.2 (15.1–35.2)	22.4 (14.9–30.5)	0.039
Diabetes mellitus, n (%)			0.155
Absent	337 (90.6)	43 (97.7)	
Present	35 (9.4)	1 (2.3)	
Preoperative biliary drainage, n (%)			0.700
Absent	41 (11.0)	4 (9.1)	
Present	331 (89.0)	40 (90.9)	
Preoperative cholangitis, n (%)			0.655
Absent	315 (84.7)	39 (88.6)	
Present	57 (15.3)	5 (11.4)	
Type of hepatectomy, n (%)			0.726
Left-sided hepatectomy	223 (60.0)	24 (54.5)	
Right-sided hepatectomy	140 (37.6)	19 (43.2)	
Others	9 (2.4)	1 (2.3)	
Combined vascular resection, n (%)			0.257
Absent	212 (57.0)	29 (65.9)	
Present	160 (43.0)	15 (34.1)	
Division level of the common bile duct, n (%)			< 0.001
At pancreatic entry	312 (83.9)	21 (47.7)	
At intrapancreatic level	60 (16.1)	23 (52.3)	
Operative time [min]	548 (319–1005)	581 (430–978)	0.039
Blood loss [ml]	1015 (46–10,349)	1113 (352–5560)	0.243
Blood transfusion, n (%)			0.420
Absent	266 (71.5)	34 (77.3)	
Present	106 (28.5)	10 (22.7)	

Values are shown as number (%) or median (range)

Bold values indicate statistical significance ($P < 0.05$)

of drain fluid culture on days 1, 3, and 7 were higher in patients with POPF than in those without POPF, although the differences were statistically marginal. Transient elevation of serum amylase was observed in 52.9% (220/416) of the patients; however, no patients exhibited signs of acute pancreatitis. The occurrence of intra-abdominal abscess and liver failure was significantly higher in patients

Table 2 Postoperative outcomes according to with or without clinically relevant pancreatic fistula

Variables	Pancreatic fistula		<i>P</i>
	Without (<i>n</i> = 372)	With (<i>n</i> = 44)	
Drain amylase value [IU/L]			
POD 1	448 (35–63,103)	2756 (78–16,148)	< 0.001
POD 3	90 (0–87,906)	232 (40–74,265)	< 0.001
POD 7	68 (8–43,369)	380 (20–64,000)	< 0.001
Positive rate of drainage fluid culture, <i>n</i> (%)			
POD 1*	28 (7.6)	7 (16.3)	0.075
POD 3 [†]	41 (11.4)	9 (22.0)	0.076
POD 7 [‡]	86 (25.7)	17 (38.6)	0.074
Bile leakage (grade B), <i>n</i> (%)			0.341
Absent	285 (76.6)	37 (84.1)	
Present	87 (23.4)	7 (15.9)	
Liver failure (grade B, C), <i>n</i> (%)			0.006
Absent	309 (83.1)	29 (65.9)	
Present	63 (16.9)	15 (34.1)	
Intra-abdominal abscess, <i>n</i> (%)			< 0.001
Absent	315 (84.7)	15 (34.1)	
Present	57 (15.3)	29 (65.9)	
Intra-abdominal bleeding, <i>n</i> (%)			0.163
Absent	367 (98.7)	42 (95.5)	
Present	5 (1.3)	2 (4.5)	
Non-surgical reoperation, <i>n</i> (%)			1.000
Absent	328 (88.2)	39 (88.6)	
Present	44 (11.8)	5 (11.4)	
Reoperation, <i>n</i> (%)			0.286
Absent	364 (97.8)	42 (95.5)	
Present	8 (2.2)	2 (4.5)	
Duration of drain placement [#] [days]	7 (4–40)	31 (22–113)	< 0.001
Hospital stay [days]	24 (6–202)	35 (23–156)	< 0.001
90-day mortality, <i>n</i> (%)	5 (1.3)	1 (2.3)	0.491

Values are shown as number (%) or median (range)

Bold values indicate statistical significance ($P < 0.05$)

[#]data on the drain placed behind the pancreas head

Note that fluid culture was not performed in *3 patients, [†]16 patients, and [‡]37 patients, respectively

with POPF. There were 15 patients who experienced POPF only without other complications. The duration of drain placement and hospital stay were also significantly longer in patients with POPF.

Intra-abdominal bleeding occurred in 7 (1.7%) patients, including 5 patients without POPF and 2 patients with POPF. In the latter 2 patients, bleeding came from a pseudoaneurysm caused by POPF (one in the right hepatic artery and the other in the gastroduodenal artery), which was successfully treated with transcatheter arterial embolization.

Mortality (90 days) was 1.4% (6/416) in all cohorts, with no difference between the patients with POPF and those without POPF (Table 2). One patient (an 80-year-old male) with POPF died of aspiration pneumonia on day 29 after surgery, which was not related to POPF. Two patients with POPF were readmitted due to cholangitis within 90 days after surgery, although there was no 90-day rehospitalization related to POPF.

Risk factors for clinically relevant POPF

Three pre- or intraoperative clinical variables with $P < 0.1$ in the univariable analysis were used for the multivariable analysis (Table 3). A BMI of ≥ 22 and intrapancreatic resection of the common bile duct following the excavation of the pancreas were identified as independent risk factors for POPF in surgery for PHCC.

Discussion

The present study first showed that approximately 10% of patients who underwent resection for PHCC had clinically relevant POPF and that high BMI and excavation of the pancreas were independent risk factors of POPF. Bile leakage, bleeding, and liver failure are well-known major complications in hepatobiliary resection [17]. POPF should also be noted as a major complication in surgery for PHCC, in which extrahepatic bile duct resection with lymphadenectomy is routinely performed. One previous study [7] reported that POPF occurred in 19 (8.8%) of 217 patients who underwent resection of hilar malignancy and that intrapancreatic resection of the bile duct was a risk factor for POPF. These findings were compatible with the present observations, but amylase levels of abdominal drain fluid were not presented in that study [7].

Several authors have reported POPF in patients with gastric cancer who underwent gastrectomy with lymphadenectomy [18–22]. In this surgery, the extrahepatic bile duct is preserved, but pancreatic parenchymal injury may occur during peripancreatic lymph node dissection. According to the previous reports [18–22], the incidence of POPF in gastrectomy is 4–18%, and high BMI or excessive visceral fat is reported as a risk factor for POPF, which is compatible with the present study. These findings imply that it is somewhat difficult to distinguish the

Table 3 Univariable and multivariable analyses for clinically relevant pancreatic fistula

Variables	n	With POPF (%)	Univariable P	Multivariable	
				Odds ratio (95% CI)	P
Body mass index [kg/m ²]			0.017		0.032
< 22	249	19 (7.6)		1	
≥ 22	167	25 (15.0)		2.07 (1.06–4.02)	
Operative time [min]			0.065		0.205
< 540	177	13 (7.3)		1	
≥ 540	239	31 (13.0)		1.58 (0.78–3.23)	
Division level of common bile duct			<0.001		<0.001
At pancreatic entry	333	21 (6.3)		1	
At intrapancreatic level	83	23 (27.7)		5.61 (2.89–10.90)	

Bold values indicate statistical significance ($P < 0.05$)

POPF postoperative pancreatic fistula, CI confidence interval

pancreatic parenchyma from the surrounding fat tissue, including lymph nodes, in fatty patients. In the present study, ROC curve analysis revealed the optimal cutoff value of BMI was 22. This cutoff value was surely not high compared to the Western cohort. However, the proportion of patients with BMI > 25, which is categorized as high BMI, was minor in the present cohort. The cutoff value of BMI may be different among studies. Importantly it is evident that the more obese, the more risky for POPF.

R0 resection is the only way to offer long-term survival in patients with PHCC. Due to downward cancer extension, therefore, the common bile duct is sometimes divided at the intrapancreatic level [1, 2]. When the examination of an intraoperative frozen section of the distal ductal margin is positive, an additional bile duct resection following the excavation of the pancreas is also performed [11]. These procedures inevitably injure the pancreatic parenchyma and carry a risk for POPF. In fact, 23 (27.7%) of the 83 patients who underwent resection of the intrapancreatic bile duct developed POPF.

A recent randomized study reported the superiority of a no-drain policy in pancreatic surgery [23], finding that the incidences of POPF and POPF-related complications were significantly lower in the no-drain group than in the drain group. A rationale for omitting the drain is that the drain placement itself may provide access for bacteria, potentially leading to an infection of the intra-abdominal fluid collection. On the other hand, another randomized study observed that pancreatoduodenectomy without drain placement increased the incidence and severity of postoperative complications [24]. The present authors routinely place three prophylactic drains in surgery for PHCC and pay careful attention to drain management after surgery. Although the morbidity rate was similar to other studies, the mortality rate was much lower compared to other studies [3, 25–27]. These findings may justify our perioperative drain management. Meticulous dissection of the

lymph nodes and intrapancreatic bile duct is essential to prevent pancreatic injury. In addition, it is important to place drains adequately in order to avoid critical complications secondary to POPF. Covering the defect of the pancreas using the round ligamentum during surgery [28] or postoperative administration of somatostatin analogue [29] may decrease the incidence of POPF.

The main limitation of this study was its retrospective nature, the small number of patients with POPF, and the fact that it was a single-centre study. However, the number of resections in patients with PHCC is inherently small. In addition, due to the scarcity and absence of awareness about POPF, it will be difficult to conduct a study with a large sample size. In spite of some limitations of this study, we believe that the results presented here are reasonable and convincing.

In conclusion, POPF occurs in approximately 10% of patients who undergo resection for PHCC. Careful postoperative management with attention to POPF is required, especially in patients who undergo intrapancreatic resection of the common bile duct and in those with a high BMI.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Informed consent Informed consent was obtained from all participants included in this study.

Ethical approval The study was approved by the institutional review board.

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